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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,611	11/30/2001	Jun-Ichi Nezu	06501-094001 / C2-103 PCT	1877

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/20/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,611	NEZU ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-92* is/are pending in the application.

4a) Of the above claim(s) *16-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *55-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed on 06/09/2003 has been entered. Claims 1-15 have been canceled. Claims 16-54 are withdrawn. Claims 55-92 have been added. Claims 16-92 are pending and claims 55-92 are under consideration in the instant action.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-15 in Paper No. 12 is acknowledged. Claims 16-54 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12. Claims 55-92 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic postnatal mouse comprising a heterozygous disruption in the LKB1 gene as a result of recombinase mediated gene disruption prior to embryogenesis, wherein the mouse exhibits digestive tract polyposis, does not reasonably provide enablement for 1) any species of transgenic non-human mammal comprising a homozygous disruption in the LKB1 gene or 2) any species of transgenic non-human mammal comprising a disruption of the

endogenous LKB1 gene wherein the disruption is induced postnatally or 3) a transgenic non-human, postnatal mouse comprising a disruption in the LKB1 gene as a result of recombinase mediated gene deletion prior to embryogenesis, wherein the mouse exhibits pigmental spot formation on mucous membrane or skin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The previous rejection of claims 1-15 is maintained as it applies to newly added claims 55-92, which are drawn to similar subject matter, for the reasons of record advanced on pages 2-8 of the previous office action mailed 12/09/2003 and reiterated below.

1) Applicant argues that the rejection based on the specification failing to enable using a transgenic non-human mammal that does not display a phenotype is not relevant to the pending claims as the claims now recite a phenotype for both homozygous (claims 55-83) and heterozygous (claims 84-92) transgenic non-human mammals comprising an induced disruption in the LKB1 gene. Applicant's argument is not persuasive.

With respect to claims 55-83, Applicant more specifically argues that the homozygous mammal has a phenotype of embryonic lethality. While support for this phenotype is found in the specification (page 26), the specification fails to teach how one of skill in the art would use a mammal exhibiting embryonic lethality. The specification teaches prophetically, using the mammals of the invention to screen candidate pharmaceutical agents. The specification does not suggest screening pharmaceutical agents using embryos. The specification does not teach how one would perform such a task using a non-viable mammal. Furthermore, claims 67 and 69-83 continue to encompass heterozygous non-human mammals exhibiting any phenotype. While

claim 67 adds the limitation of wherein the progeny of the heterozygous non-human animal that are homozygous for the engineered disruption are embryonic lethal, the claim fails to recite a phenotype for the heterozygous mammal itself and thus encompasses said animal with any phenotype, including wildtype. As set forth on page 6, paragraph 3 of the previous office action, the specification does not enable making and/or using a mammal heterozygous for an LKB1 gene disruption wherein the mammal exhibits any phenotype.

With respect to the mammals of claims 84-92 wherein the LKB1 gene or regulatory region has been disrupted postnatally, applicant points out that the claims now require the phenotype of exhibiting digestive tract polyposis or pigmental spot formation on mucous membrane or skin. Support for this phenotype in the claimed mammal is not found in the specification. Applicant points to page 1, lines 9-11 and page 9, lines 20-23 as supporting the claimed phenotype. These references, however, are prophetic, as the specification does not teach that the animals even form polyps or pigment macules. As set forth in the previous office action (pages 3-5) the phenotype of transgenic mammals is unpredictable and it cannot be predicted based on the teachings of the specification that the claimed transgenic non-human mammals will develop the claimed phenotypes. The specification did not teach any characteristics of the claimed mammals or that the mammals claimed developed digestive tract polyposis or pigmental spot formation on mucous membrane or skin as expected.

Applicant argues further that the claimed phenotype of polyposis in the digestive tract or pigmental spot formation on mucous membranes or skin in the claimed heterozygous mice (claims 84-92) has been confirmed by post-filing art (see Applicant's response, page 9, paragraph 1). Claims 84-92 encompass mammals comprising either a homozygous or

heterozygous disruption induced postnatally wherein the mammal exhibits digestive tract polyposis or pigmental spot formation on mucous membrane or skin. The post-filing art cited by applicant (see applicant's response, page 9, paragraph 1) teaches generating mice with a heterozygous disruption of the LKB1 gene wherein the disruption leads to polyposis and wherein the gene disruption is introduced prior to embryogenesis (Rossi, page 12328, column 2, paragraph 2; Jishage, page 5905, column 2, paragraph 2-page 5906, column 1; Bardeesy, page 162, column 2, paragraph 4). The art does not teach a phenotype of pigmental spot formation on mucous membrane or skin, does not teach the claimed phenotype for homozygous mice, and does not teach postnatal disruption of the LKB1 gene. Because the mice of the post-filing art differ from the claimed mammals wherein the LKB1 gene disruption is induced postnatally (refer to claim 84, line 3), the post-filing art does not correlate to claims 84-92.

Therefore, in light of the post-filing art, the specification is enabling for a transgenic postnatal mouse comprising a heterozygous disruption in the LKB1 gene as a result of recombinase mediated gene deletion prior to embryogenesis, wherein the mouse exhibits digestive tract polyposis but not the full breadth of the claims.

2) With respect to the rejection based on the lack of guidance to target gene insertions in any species of mammal other than mouse, applicant argues targeted gene insertion was available for rabbits, sheep and pigs. Applicant references Hammer et al, 1985 and Roschlau et al, 1989 as well as USPN 5,487,992. With respect to Hammer and to Roschlau, these references do not teach targeted gene insertion but teach random transgene insertion. The instant invention requires targeted transgene insertion of a conditional allele into the LKB1 gene. USPN 5,487,992 teaches targeted transgene insertion in mouse ES cells followed by generation of transgenic mice with

said ES cells. USPN 5,487,992 does not teach this technique for any other species. Applicant argues that knockout technology was not limited to ES cells because somatic cells could also be used to make mice comprising gene-targeted disruptions (McCreath, June 2000, Nature 405:1066-1069). Applicant's argument is not persuasive because McCreath (June 2000) was not available to one of skill in the art at the time the invention was made (May 2000).

3) With respect to the rejection based on the lack of guidance as to how to introduce Cre-recombinase to a postnatal embryo after the period of lethality has passed (pages 6-7 of the previous office action), applicant argues the teachings in the specification at page 8, lines 7-16 enables one of skill in the art to disrupt a gene postnatally. Applicant's argument is not persuasive. It was well known in the art at the time of filing that recombinase-mediated gene disruption can be induced postnatally, however, introduction of the recombinase is spatially and temporally specific for various methods of introduction. For example, the specification teaches that DNA expression vectors can be used to introduce Cre or transgenic animals comprising a Cre expression vector can be used to introduce a Cre transgene by mating. Different expression vectors will lead to different patterns of Cre expression, resulting in Cre-mediated recombination in various tissue and cell types at different times, each pattern being specific to the vector used. The specification fails to provide any guidance as to where or when Cre should be expressed to obtain the claimed transgenic mammals exhibiting the claimed phenotype or which vector to use to obtain said mammal. Without knowing where and when recombinase-mediated gene disruption should occur, it would require undue experimentation for a skilled artisan to determine how to introduce Cre-recombinase in a manner to prevent embryonic lethality and obtain digestive tract polyposis or pigmental spot formation on mucous membrane or skin.

4) With respect to the rejection based on the specification failing to provide the guidance necessary to identify and target a regulatory region of the LKB1 gene (claims 84 and 86-92), Applicant argues that one of ordinary skill in the art would know to target a region upstream of the LKB1 coding region and that no more than routine experimentation would be necessary assay for a decrease in LKB1 expression or activity as a result of the targeting (see page 11 of Applicant's response). The specification does not teach that the LKB1 regulatory regions are upstream of the coding region of the gene. It is known in the art that regulatory regions can be close to or far from the coding region of a gene and in some cases they are downstream of the gene or within introns. Determining the location of gene regulatory elements has been recognized as one of the major challenges in bioinformatics (Rombauts, 2003, Plant Physiology, Vol. 132, pp. 1162-1176). Furthermore, a mere decrease in expression or activity of LKB1 caused by targeted transgene insertion into a regulatory element cannot be predicted to cause the claimed phenotypes. The specification does not teach the location of the LKB1 regulatory regions, how many regulatory elements there are, or the respective activity of each element and does not teach how much of a reduction in LKB1 expression or activity must be obtained to generate the desired phenotypes.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of now canceled claims 1-15 under 35 USC 112 is withdrawn. New grounds of rejection of the newly added claims 55,67,77 and 84 appear below.

Claims 55,67,77 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 is unclear because the claim does not clearly set forth how the gene is genetically altered and does not recite a description of the disruption.

Claim 55 recites the limitation "both copies" in line 3. There is insufficient antecedent basis for this limitation in the claim. An animal may have only 1 copy.

Claim 67 recites the limitation "the transgenic non-human animal" in line 3. There is insufficient antecedent basis for this limitation in the claim. The claim is drawn to a transgenic non-human mammal.

Claim 67 is unclear because it fails to discern whether the progeny of the transgenic non-human animal are homozygous for the engineered disruption or whether it is the transgenic non-human animal that is homozygous for the disruption. If the latter is the case, then it is not clear whether the progeny must be homozygous or heterozygous for the disruption to exhibit embryonic lethality.

Claim 77 recites the limitation "both alleles" in line 1. There is insufficient antecedent basis for this limitation in the claim. An animal may have only 1 allele of a gene.

Claim 84 is unclear. The phrase “target sequences of a recombinase” in lines 3-4 is unclear. The phrase “recombinase target sequences” is clearer. The phrase “postnatally mammal” in line 3 is grammatically incorrect.

Claim 84 recites the limitation "the recombinase-mediated deletion" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim. Furthermore, the phrase does not clearly set forth the step required in the process used to make the product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claim 1 under 35 USC 102 (b) is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 1-15 under 35 USC 103 (a) is withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

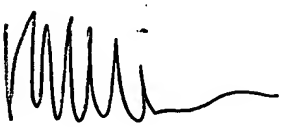
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Examiner
Art Unit 1632



MICHAEL WILSON
PRIMARY EXAMINER